AMENDMENTS TO THE DRAWINGS

The attached sheets of drawings include changes to Figs. 2B, 2C2, 2C4, 3A, 3C, 3D, 4A6, and 5A. These sheets replace the original sheets. These figures have been conformed to the informal drawings as originally filed in PCT/US00/12371 on May 5, 2000, to which the instant application relates back, as follows:

Fig. 2B - "sec" has been re-spelled;

Fig. 2C2 - "sec" has been re-spelled;

Fig. 2C4 - "sec" has been re-spelled;

Fig. 3A - "ratio" has been re-inserted on the y axis;

Fig. 3C - "sec" has been re-spelled;

Fig. 3D - "CI" has been re-inserted on the y axis;

Fig. 4A6 - "Seconds" has been re-spelled; and

Fig. 5A - "cpm on 5 x 10^6 monocytes" has been re-inserted on the y axis.

REMARKS

Applicant wishes to thank Examiner Kemmerer for the courtesy extended to the inventors, Drs. JiMing Wang and Joost Oppenheim, and the representative, Nancy Vensko, attorney of record, on October 16, 2003. The Interview Summary Form PTOL-413 summarizes the discussions held at the personal interview. The present response to the outstanding Office Action includes the substance of the Examiner Interview.

A. Disposition of Application

By this amendment, Applicant has canceled Claims 1-4 (as being withdrawn from consideration) and 6-10, all without prejudice, amended Claims 5 and 11-13, and added Claim 14. Thus, Claims 5 and 11-14 are pending. This amendment is presented to make explicit that which was implicit in Claim 5. Additionally, per MPEP 608.01, the Specification has been amended to delete the embedded hyperlink. Furthermore, in accordance with the Examiner's suggestion, the title has been amended to be more descriptive. Finally, the claims have been amended to delete the recitation of non-elected subject matter (e.g., T21/DP107). Turning to the figures, Figs. 2B, 2C2, 2C4, 3A, 3C, 3D, 4A6, and 5A have been conformed to the informal drawings as originally filed in PCT/US00/12371 on May 5, 2000, to which the instant application relates back. No new matter has been added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

B. Compliance with 35 USC 112/1

The Patent Office rejected Claims 5-12 under 35 USC 112/1 on the stated ground that the Specification, while being enabling for use of T20/DP178 of SEQ ID NO:197 does not reasonably provide enablement for use of generic variants thereof. According to MPEP 2164.08, enablement must be commensurate in scope with the claims. As disclosed in the Specification and the post-filing date art of record, Su et al., Blood 93: 3885 (1 June 1999), the investigators made the discovery that T20/DP178 is an activator of the human phagocyte formyl peptide receptor (FPR) and thus contemplate T20/DP178 and its analogs as FPR agonists and antagonists useful in modulation of the immune response. Initially, T20/DP178 was shown to be a chemoattractant and activator of monocytes and neutrophils. Human monocytes and neutrophils migrated in a dose-dependent manner in response to T20/DP178 (Spec. at Fig. 1A). The migration of monocytes and neutrophils to T20/DP178 was completely inhibited by pretreatment of the cells with pertussis

toxin, but not cholera toxin (Spec. at Fig. 1B), indicating that a G-protein coupled receptor was involved. This was supported by induction of a dose-dependent and pertussis toxin-sensitive calcium mobilization in monocytes and neutrophils by T20/DP178 (Spec. at Fig. 2A and B). The bacterial chemotactic peptide fMLP had a marked desensitizing effect on T20/DP178-induced calcium mobilization in both monocytes and neutrophils (Spec. at Fig. 2C). The desensitization of calcium flux between fMLP and T20/DP178 was unidirectional when both agonists were used at the same concentration. These results indicated that T20/DP178 shares the formyl peptide receptor with fMLP identified on human phagocyte cells.

T20/DP178 was shown to be a functional ligand for the formyl peptide receptor (FPR) on phagocyte cells. T20/DP178 induced a dose-dependent calcium mobilization in cells transfected to express the FPR (Spec. at Fig. 3A). Sequential stimulation of cells transfected to express the FPR with fMLP and T20/DP178 or vice versa resulted in bidirectional desensitization (Spec. at Fig. 3B). Neither T20/DP178 nor fMLP stimulated calcium flux in parental cells or mock-transfected cells (Spec. at Fig. 3C), indicating that the response was indeed mediated by the FPR. In chemotaxis assays, while cells transfected to express the FPR could be induced by fMLP to migrate, T20/DP178 also induced pronounced migration of the cells transfected to express the FPR (Spec. at Fig. 3D). In contrast, T20/DP178 or fMLP did not induce migration of mock-transfected cells (Spec. at Fig. 3E). Ligand binding competition experiments with labeled fMLP indicated that T20/DP178 effectively competed with labeled fMLP for binding to cells transfected to express the FPR (Spec. at Fig. 3F), confirming that T20/DP178, like fMLP, is acting at the FPR. Further demonstration of the FPR agonist activity of T20/DP178 was shown by rapid phosphorylation of the FPR after stimulation of cells transfected to express the FPR with T20/DP178 (Spec. at 13:20-27), which was identical to the effect detected in fMLP-treated cells. Furthermore, T20/DP178 induced activation of MAP kinase in human monocytes (Spec. at 13:28-14:8), a signaling event similarly initiated by fMLP.

Analogs of T20/DP178 acted as FPR antagonists. Four T20/DP178 analogs that lack 3, 5, 7, and 12 amino acids, respectively, at the N-terminus of T20/DP178 were tested. All of these analogs failed to induce significant calcium mobilization in monocytes (Spec. at Fig. 4A) or cells transfected to express the FPR (Spec. at Fig. 4B). Instead, they abolished calcium mobilization in response to subsequent T20/DP178 or fMLP stimulation in both monocytes and cells transfected to

express the FPR (Spec. at Fig. 4A and B). The synthetic T20/DP178 analogs also specifically inhibited labeled fMLP binding (Spec. at Fig. 5A) and significantly attenuated migratory response of cells transfected to express the FPR induced by T20/DP178 and fMLP (Spec. at Fig. 5B). These results indicate that amino truncations of 3 to 12 amino acids from 36 amino acid T20/DP178 yielded FPR antagonists.

The FPR has a capacity to interact with a great variety of ligands. Per Su et al., Blood 93: 3885 (1 June 1999), at paragraph bridging p. 3889 and 3890, a major advance in the study of leukocyte motility was the discovery of synthetic N-formyl oligopeptide chemoattractants for phagocytes. Several natural N-formyl peptide chemoattractants, including the prototype formyl-methionyl-leucyl-phenylalamine (fMLP), have since been purified from bacterial supernatants, providing evidence that they are biologically relevant ligands for the FPR. Mitochondrial proteins are also N-formylated and are chemotactic for neutrophils bearing the FPR, representing a possible source of endogenous agonist(s). Although early studies indicated that the N-formyl group was essential for optimal agonist potency, recent studies have shown that nonformylated peptides may also bind the FPR and activate phagocyte function. The synthetic pentapeptide Met-Nle-Leu-Phe-Phe-OH, either N-formylated or N-actetylated, is more potent that the parental prototype fMLP (trimer) in the induction of calcium flux in human neutrophils. Amino terminal urea-substituted and carbonate-modified peptides are also potent agonists for the FPR. In addition, altering the amino acid composition of these peptides can convert an agonist to an antagonist. In the present experiments, the non-N-formylated T20/DP178 does not bear any sequence identity to the reported FPR agonists yet showed potent FPR stimulating activity. Furthermore, the nonacetylated T20/DP178 was equally active as the acetylated form, indicating that acetylation is not a requirement for T20/DP178 to stimulate the FPR. The present investigators also observed that deletion of several amino acids from the N-terminus of T20/DP178 yielded FPR antagonists. Thus, the spectrum of interaction between FPR and its agonists and antagonists is broad, for the binding pocket of this receptor appears to enable it to accommodate a great variety of ligands.

In sum, T20/DP178 was shown to be a functional ligand for the formyl peptide receptor (FPR) on phagocyte cells. Analogs of T20/DP178 acted as FPR antagonists. The FPR has a capacity to interact with a great variety of ligands. As required by the MPEP 2164.08, enablement

is fully commensurate in scope with the claims. The Specification is enabling not only for use of T20/DP178 of SEQ ID NO:197 but also for use of its generic variants as defined in the claims.

C. Compliance with 35 USC 102(b)

The Patent Office rejected Claims 5 and 13 under 35 USC 102(b) as being anticipated by Lawless et al., Biochemistry 35: 13697 (1996). Lawless et al. describes T20/DP178 as a potent inhibitor of HIV-mediated cell-cell fusion. According to MPEP 2113, product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. In In re Thorpe (citation omitted), the claim was directed to a color developer. The process of making the developer was allowed. The product-by-process claim was rejected because the end-product, in both the prior art and the allowed process, ended up producing the color developer. In contrast, here in the instant application, a process is being claimed, not a product-by-process. Just as the process of making the developer was allowed in In re Thorpe, the process of screening for agonists and antagonists should be allowed in the instant application. All dependent claims herein relate back to Claim 5. As Claim 5 has been amended to make explicit that which was implicit to recite the steps of screening for agonists and antagonists, the present set of claims is free of the cited art.

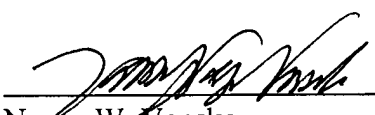
CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the below-given telephone number.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 11/3/03

By: 

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